UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/337,584	06/21/1999	ARTHUR M. KRIEG	C1039/7020-H	9169

7590 03/29/2006

HELEN C LOCKHART
WOLF GREENFIELD & SACKS PC
600 ATLANTIC AVENUE
BOSTON, MA 02210

EXAMINER	
MINNIFIELD, NITA M	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 03/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/337,584	KRIEG ET AL.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-47,49-53,56,57,82-85,90,92,94,96,98,100,102 and 103* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-47,49-53,56,57,82-85,90,92,94,96,98,100,102 and 103* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892) 3 pgs

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *attached*.

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 27, 2005 has been entered.

2. Claims 42-47, 49-53, 56, 57, 82-85, 90, 92, 94, 96, 98, 100, 102 and 103 are now pending in the present application. All rejections have been withdrawn in view of Applicants' comments, with the exception of those discussed below.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 42-47, 49-53, 56, 57, 82-85, 90, 92, 94, 96, 98, 100, 102 and 103 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating asthma in a subject, murine model, comprising administering to an asthmatic subject an immunostimulatory nucleic acid (CpG, specifically SEQ ID NO: 10), does not reasonably provide enablement for a method for treating asthma in a subject, animal or human, comprising administering to an asthmatic subject an immunostimulatory nucleic acid (CpG, the scope of the myriad possible immunostimulatory nucleic acids encompassed by the formulas as set forth in claims 42, 49, 90, 92, 94 and 96 for example) and the

CpG sequences defined by SEQ ID NO: 3, 7, 12, 38 or 57. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a method for treating asthma in a subject comprising administering to an asthmatic subject in need of such treatment a composition comprising a CpG oligonucleotide (8-100 or 8-40 nucleotides long). The CpG oligonucleotide formulas are 5'X_1 X_2CGX_3X_4 3'. The claims, for example, define that X_1, X_2, X_3, and X_4 are any nucleotide. The claims define that the nucleic acid phosphate backbone has been modified. The routes of administration and delivery formulations have been defined as well as specific CpG sequences, SEQ ID NO: 3, 7, 10, 12, 38 and 57.

The specification discloses Example 12 (see pp. 63-64), prevention of the development of an inflammatory cellular infiltrate and eosinophilia in a murine model of asthma. Mice were immunized with *Schistosoma mansoni* eggs (SEA) by i.p. injection on days 0 and 7. SEQ ID NO: 10 was administered to the immunized mice and soluble SEA was administered by intranasal instillation on days 14 and 21. After challenge the mice were sacrificed and cytokine levels and other assays conducted on the lavage fluids. The specification indicates that Figures 9-15 show that CpG/SEA induced inflammatory cells, eosinophils, to be present and generated macrophages; higher IL-12 was induced, IL-4 was reduced and IFN-gamma production increased. Applicants assert that the CpG redirected the cytokine response of the lung to production of IL-12 and IFN-gamma, indicating a Th1 type immune response (p. 65).

The specification does not teach that any of the other myriad of possibilities of CpG having the claimed SEQ ID NOs or the claimed formulas can be used to treat an asthmatic subject, animal or human. The method of Example 12 teaches that CpG and the SEA were administered to the asthmatic subject at the same time. It is noted that Table 5 in the specification shows an *in vivo* (mice) increase in Th1 type cytokines (IL-6, IL-12, TNF, IFN, GMCSF). However, it is not clear that the other claimed CpG sequences are sufficient to treat an asthmatic subject. The specification teaches *in vitro* methods and *in vivo* methods using SEQ ID NO: 10 in a murine model for asthma. It is not clear from the specification that the scope of the claimed invention is enabled.

The state of the art is unpredictable with regard to asthma treatments using CpG. CpG containing oligonucleotides are currently being investigated for exerting their immunotherapeutic effects in various organisms. Biological responses to the administration of CpG containing oligonucleotides vary, however, depending on the mode of administration and the organism (see McCluskie et al Molecular Med., 1999, 5/5:287-300 in its entirety, and especially on p. 296). The state of the art, taken as a whole, is still unpredictable with regard to the use of ISS-ODN in treating asthma in an asthmatic subject (human or otherwise) in need of such treatment.

The amount of direction or guidance presented in the specification and the presence or absence of working examples is a hindrance to practicing the claimed invention. Applicants have not provided guidance in the specification toward a method for treating asthma comprising the administration of *any* immuno-stimulatory nucleic acid comprising the formula set forth in claim 42, for example. As previously stated the specification teaches an increase in immunomodulation in

mice (and comprising conversion from a Th2 to a Thl immune response), and treatment of asthma in a mouse model comprising the administration of SEQ ID NO: 10 and antigen (SEA). One skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of the successful treatment of asthma in any organism comprising the administration by *any* route of *any* immunostimulatory nucleic acid comprising the formula in the claims in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the biological effects exerted by CpG containing oligonucleotides in any and/or all organisms/subjects. The specification as filed fails to provide particular guidance which resolves the known unpredictability in the art associated with effects provided *in vivo* in any and/or all organisms upon administration via any route of CpG containing oligonucleotides, and further whereby treatment effects are provided in any and/or all organism for asthma. The breadth of the claims is very broad and the quantity of experimentation required is undue. The quantity of experimentation required to practice the invention as claimed would require the de novo determination of accessible target sites, modes of delivery and formulations of the CpG to target appropriate cells and/or tissues in any and/or all organisms/subjects, and further whereby treatment effects are provided for the claimed conditions. Since the specification fails to provide particular guidance for the treatment of asthma comprising administration by any route of any CpG containing oligonucleotide (claimed formulas), and since determination of these factors for a particular CpG containing oligonucleotide and for the particularly claimed conditions, route of administration and organism is highly unpredictable, it would require undue

experimentation to practice the invention over the broad scope as presently claimed.

The examples provided of the induction of various interleukins in spleen, liver or thymus cells are not representative of the successful treatment of asthma using any CpG containing oligonucleotide. No correlation is taught in the instant disclosure between the ability of these CpG containing oligonucleotides to induce a Th1 response in vitro (e.g. amount of IL-6 induction) and their ability to treat asthma *in vivo*. An assumed common mechanism of action does not ensure enablement for treatment. Effective delivery to appropriate and concentration of a particular CpG containing oligonucleotide necessary for providing treatment for asthma for a particular CpG containing sequence are still highly unpredictable. The success of treating asthma with SEQ ID NO: 10 is not necessarily representative or correlative of the ability to successfully treat asthma with *any* of the *generic sequences* claimed and the *myriad* possibilities of CpG sequences encompassed by the claims. The *in vivo* treatment success for these generic sequences would require undue experimentation beyond that provided in the instant disclosure.

The rejection is maintained for the reasons of record. Applicant's arguments filed ***April 14, 2005*** have been fully considered but they are not persuasive. Applicants have asserted that the specification describes a class of molecules (oligonucleotides) having a common structural motif, CpG dinucleotide, that when administered to a subject results in the immune response being altered, with a Th1 response being favored. The specification describes this as well as presents data, in vivo and in vitro, using a number of different CpG containing oligonucleotides (see Table 5). The Examiner appreciates Applicants pointing out specific descriptions and data; however, does the in vivo data from one CpG molecule, SEQ ID NO: 10, indicate that all other CpG molecules will function in the same manner (i.e. increase the Th1 response)? It appears that not all CpG

molecules increase the Th1 response. Does SEQ ID NO: 35 increase the Th1 response? What is the minimum level of cytokine (IFN-gamma and IL-12) increase necessary to indicate that a Th1 response has occurred?

Applicants have asserted that in addition to the working examples a number of studies published since the filing of the patent application have reiterated, as set forth in the specification, that CpG oligonucleotides having different structures but maintaining the critical CpG motif result in an altered immune response (see US Patent Application SN 10/644052 corresponding to PCT Publication No WO2004/016805 and Hemmi et al, 2002). However, these publications are after Applicants' filing date of October 30, 1996. Applicants' specification and claims should be enabled at the time of filing.

Applicants have asserted that the CpG containing molecules can be used in a method for treating asthma comprising administering the CpG alone and that the specification includes 14 tables of data in addition to the 15 figures of data, in vitro or in vivo, without the concurrent use or administration of an antigen. It is not clear to the Examiner which tables and figures show in vivo enablement for asthma using CpG other than SEQ ID NO: 10. Please note that the rejection is a 112, first paragraph rejection with regard to scope of enablement, not a total lack of enablement. Further, as previously stated, the state of the art indicates that not all CpG containing molecules work on all organisms (see McCluskie et al 1999).

Applicants have asserted that the specification teaches methods for treating asthma in terms of the administration of CpG as a therapeutic. The immune profile, which is consistent with the promotion of a Th1 favored response, is important in asthma. Applicants have indicated that Tables 5 and 13 provide data that show CpG alone (without antigen/allergen) produced a Th1 biased cytokine induction. A review of Table 13 shows that CpG is not a consistent inducer of cytokines, which have the ability to induce a Th1 response. There was induction of IL-12 for the CpG molecules tested in the first experiment, however only one CpG molecule induced IL-12 in the second experiment. The CpG molecules do not appear to be consistent in their function.

It is noted that Applicants have provided several references (Lukacs et al, 1994, 1996, and Padrid, et al 1998) that indicate that there is a murine animal model for asthma. Airway inflammation is induced by administering schistosome egg antigen (SEA) in vivo to the animal as a model of asthma. The SEA induces a Th2 response in mice and elicits an inflammatory reaction in lungs. Applicants have asserted that this model was used in Example 12 of the specification, and that the use of CpG oligonucleotides alone is useful as a therapy for asthma. However, it is noted that only CpG, SEQ ID NO: 10, was administered to mice, not the full

scope of any of the myriad CpG containing molecules that are envisioned in the specification.

Applicants have asserted that 10/644052 demonstrates that CpG administered alone is effective in treating the asthmatic response (see Examples 22, 25 and 26, for example). However, as previously noted 10/644052 is evidence of enablement post filing; the specification must be enabled at the time of filing, particularly in view of the state of the art regarding the claimed invention. Further, were the experimental protocols set forth in 10/644052, specifically Examples 22, 25 and 26, the same manner as the experimental protocols of the pending application?

Applicants have asserted that several Phase I and II studies have been performed in humans to date. In particular subcutaneous administration, like that in the Satoh reference, has been performed in humans for a cancer trial. However, the pending claims are directed to treatments for asthma and allergies, not cancer.

Further, Van Uden et al (J. Allergy Clin. Immnol., 1999, 104:902-910) teaches that although "ISS are generally considered by researchers in this field to be modular 6-mer units, it has been difficult to determine the minimum stimulatory motif length. One study showed that a minimum length of 18 bases was required but that a length of 22 bases gave greater activity. Another study demonstrated good activity with a 15-mer ODN. Still another study used cationic lipid transfection to show a stimulatory effect with a 6-mer ODN." (p. 904, col. 1) Van Uden et al teaches that each ISS appears to have a different minimum length because crucial flanking bases would be variably distant from the core (p. 904, col. 2). Van Uden et al indicates that the ISS *may be a promising* method of treatment/prophylaxis for allergic disease, but that there are also some potential side effects that must be considered. The "immune system is delicately balanced between immunity and tolerance, between Th1 and Th2, and between inflammation and unresponsiveness. There is always the possibility of unwanted effects of the powerful immune stimulation that ISS delivers." (p. 907, col. 2) LPS is similar to ISS, in view of this some of the same problems observed with LPS are potential problems with ISS (p. 907, col. 2). ISS could cause excessive local inflammation as seen with other powerful Th1 adjuvants, such as CFA (p. 908, col. 1).

Finally, it should be noted that whether the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The initial inquiry is into the nature of the invention, i.e., the subject matter to which the claimed invention

pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art.

The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. See MPEP § 2164.05(b).

The state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. The state of the prior art is also related to the need for working examples in the specification.

The state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on January 2, 1990, would not have been enabled. However, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each application based on its filing date.

35 U.S.C. 112 requires the specification to be enabling only to a person "skilled in the art to which it pertains, or with which it is most nearly connected." In general, the pertinent art should be defined in terms of the problem to be solved rather than in terms of the technology area, industry, trade, etc. for which the invention is used.

The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. > Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1325-26 (Fed. Cir. 2004) ("a patent document cannot enable technology that arises after the date of application").< Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. In re Gunn, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); In re Budnick, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976) (In general, if an applicant seeks to use a patent to prove the state of the art for the purpose of the enablement requirement, the patent must have an

issue date earlier than the effective filing date of the application.). While a later dated publication cannot supplement an insufficient disclosure in a prior dated application to make it enabling, applicant can offer the testimony of an expert based on the publication as evidence of the level of skill in the art at the time the application was filed. Gould v. Quigg, 822 F.2d 1074, 1077, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987).

In general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling. Exceptions to this rule could occur if a later-dated reference provides evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. In re Hogan, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977). If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993) an article published 5 years after the filing date of the application adequately supported the examiner's position that the physiological activity of certain viruses was sufficiently unpredictable so that a person skilled in the art would not have believed that the success with one virus and one animal could be extrapolated successfully to all viruses with all living organisms. Claims not directed to the specific virus and the specific animal were held nonenabled.

The rejection is maintained for the reasons of record. Applicant's arguments filed December 1, 2005 have been fully considered but they are not persuasive. The declarations of Krieg and DeSanctis under 37 CFR 1.132 filed December 1, 2005 are insufficient to overcome the rejection of claims 42-47, 49-53, 56, 57, 82-85, 90, 92, 94, 96, 98, 100, 102 and 103 based upon 112, 1st paragraph scope of enablement as set forth in the last Office action.

With regard to the DeSanctis declaration, declarant indicated that the data obtained in the *in vivo* experiments such as those shown in Table 4 and Example 12 was consistent with the data obtained in the *in vitro* experiments, confirming that the pattern of cytokine release and Th1 effects could be exploited *in vivo*.

However, the data in both Table 4 and Example 12 shows that in each experiment there were several ODNs that had a stimulation index the same as or lower than the ODNs without a CG motif (#1982 for example). With regard to Table 13, both declarants indicated that the data shown in Table 13 involved selecting data from two different subjects to demonstrate the extremes of the data and the variability was not typical of the various CpGs tested. Declarants also indicated that one of ordinary skill in the art would have expected the type of variability seen in Table 13 and would not have altered the conclusion that CpG containing oligonucleotides would have the ability to initiate in vivo a pattern of cytokine release which would drive the immune system toward a Th1 response. However, upon review of the additional data (Krieg declaration), it is noted that there are several ODN without a CpG motif (#1471, 1745, 1845, 1908, 1911, 1944, 1957, 1958, 1982) that induced increases in the cytokine IL-12 when incubated with PBMC. Conversely, there were several ODN (#1758, 1826, 1835, 1842, 1894, 1962, 1965, 1967, 1968, 2005, 2006, 2014) with one or more than one CpG motifs where the IL-12 levels were the same as cells only or actually decreased the level of IL-12 production. Seven of the ODN without a CpG motif increased IL-12 in Patients 3 and 5. This would appear to indicate that the specification does not enable the full scope of the claims where any one of the myriad CpG will be sufficient to treat an asthmatic subject as presently claimed. Some ODNs with CpG motifs increase a Th1 type response and some don't; and there are ODNs without a CpG motif that increase a Th1 type response as well as those with a CpG motif. When a compound or composition is limited by a particular use, enablement of the claim should be evaluated based on that limitation; in this case, the myriad number of CpG oligonucleotides to treat an

asthmatic subject. It would require undue experimentation for one of ordinary skill in the art to practice the claimed invention.

Applicants have asserted that McCluskie et al is an article describing DNA vaccines against Hepatitis B virus. On page 296, the page identified by the examiner, the reference mentions that one of the factors involved in influencing the Th bias of the response to DNA vaccines is the presence of CpG motifs. The reference is not relevant to the enablement of the pending claims because the pending claims do not encompass plasmid vectors (or DNA vaccines). The pending independent claims include limitations that exclude plasmid vectors (upper size limit of 100 and phosphate backbone modification). The issues of predictability and therapeutic effectivity are very different for CpG oligo-nucleotides and DNA vaccines. However, there is no upper limit to claims 42, 56, 57, 92, 94, 98 and 96. The claims do not recite any kind of protein added in the composition of the CpG immunostimulatory nucleic acid being administered. The immunostimulatory nucleic acid could read on the whole bacteria, or the immunostimulatory nucleic acid could be part of a DNA vaccine; the claims just recite immunostimulatory nucleic acid.

Applicants have asserted that numerous working examples were provided in the specification. These examples in combination with the description in the specification were sufficient to enable one of skill in the art to practice the invention over the full scope of the claims. Consistent with the descriptions, a number of studies published since the filing of the patent application have reiterated, as set forth in the specification, that CpG oligonucleotides having different structures but maintaining the critical CpG motif result in an altered immune response. For instance, US Patent Application Serial No. 10/644,052

corresponding to PCT Publication No W02004/016805 (copy previously submitted) describes numerous examples of CpG oligonucleotides that stimulate an immune response. However, as previously noted 10/644052 is evidence of enablement post filing; the specification must be enabled at the time of filing, particularly in view of the state of the art regarding the claimed invention. Further, were the experimental protocols set forth in 10/644052, specifically Examples 22, 25 and 26, the same manner as the experimental protocols of the pending application?

With regard to the DeSanctis declaration at paragraph 15, declarant states that the CpG oligonucleotide has been tested for its therapeutic effect. Which CpG oligonucleotide is this and were the experiments to test for therapeutic effects done according to the protocols as set forth in the specification?

The Examiner acknowledges the statements in paragraph 16 that there are animal models for asthma. Applicants are encouraged to make all of the references mentioned in paragraph 16 as well as those at the end of the declaration part of the application record. Please submit copies of references as well as IDS listing these references.

With regard to the experiments and data set forth in paragraphs 17-24 of the DeSanctis declaration, were these experimental methods disclosed in the Krieg application? Any data set forth in a declaration for the purposes of showing enablement of the claimed invention should indicate that the experimental compositions, methods and/or protocols were disclosed in the specification, if such is the case.

5. Claims 42, 43, 45-47, 49-53, 56-57, 92, 94, 96, 98 and 100 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are vague and indefinite in the recitation of "immunostimulatory nucleic acid"; does Applicant intend the whole microorganism, or an isolated DNA from bacteria that contains a CpG oligonucleotide, or a synthetically made immunostimulatory nucleic acid?

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 42, 43, 45-47, 49, 50, 51, 53 and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over McMichael (5726160) taken with Pisetsky (J. Immunology, 1995, pp. 421-423).

McMichael teaches that a composition comprising prokaryotic DNA and a pharmaceutically acceptable carrier can be used to treat subjects suffering from pulmonary disease and specifically an asthmatic subject (col. 1; col. 4, example IX). McMichael does not specifically teach the claimed CpG oligonucleotide. However, Pisetsky teaches that "...the perspective on the immunologic properties of DNA has been substantially revised. This shift reflects compelling evidence that bacterial DNA, in contrast to mammalian DNA can induce a variety of responses in both normal humans as well as animals." (p. 421, right column) Pisetsky teaches that there are unmethylated CpG motifs that are found in bacterial DNA, but rarely seen in mammalian DNA; and that these DNA, CpG oligonucleotides, stimulate IL-12 and TNF production (p. 422, left column). "Structure-function studies with synthetic oligonucleotides have demonstrated that

CpG sequences flanked by two 5' purines and two 3' pyrimidines are the most potent; this motif closely resembles those that induce IFN (citation omitted). The CpG motif may have special significance as a signal, since in bacterial DNA, cytosine in not methylated, while in mammalian DNA, the content of CpG is much lower than predicted (CpG suppression). As such, bacterial DNA displays a distinctive structure, indicating the presence of foreign microorganisms (citation omitted). (p. 422, left column) "While the role of foreign DNA in innate immunity invites further inquiry, the immunologic potential of DNA has immediate relevance in the therapeutic arena." (p. 422, right column) Pisetsky teaches that DNA is a player in the immune system. In view of the combined teachings of both McMichael and Pisetsky, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the bacterial CpG oligonucleotides as taught in Pisetsky, since the art teaches that the bacterial DNA has immunological properties, for administration to an asthmatic subject as taught in McMichael to treat a pulmonary disease (asthma). McMichael teaches that prokaryotic DNA can be administered to an asthmatic subject to treat asthma. Absent any convincing evidence to the contrary, the claimed invention is prima facie obvious in view of the combined teachings of McMichael and Pisetsky.

10. No claims are allowed.

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

N. M. Minnifield
Primary Examiner
Art Unit 1645

NMM
March 16, 2006